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Gastrointestinal safety and efficacy of long-term GCSB-5 use in patients with osteoarthritis: A 24-week, multicenter study

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ABSTRACT

Ethnopharmacology relevance: A previous study indicated non-inferiority of GCSB-5 to celecoxib regarding efficacy and safety in treating OA; however, the gastrointestinal (GI) safety data was limited to 12 weeks. Accordingly, a longer term study with a larger number of patients was necessary to establish the GI safety of GCSB-5.

Aim of study: The primary goal was to determine the safety and efficacy of 24-week use of GCSB-5. The secondary goal was to compare the GI safety data of GCSB-5 with that of the previously reported Celecoxib Long-term Arthritis Safety Study (CLASS).

Method: This was a 24-week, multicenter, single-arm phase IV Study for the safety and efficacy of GCSB-5. A total of 761 patients were enrolled and 756 patients received at least one dose of GCSB-5. Among them, 629 patients (82.7%) completed the 24 week follow up. The primary goal was to determine the safety and efficacy of GCSB-5 for 24 weeks. The secondary goal was to compare the GI safety data of GCSB-5 with that of the previously reported Celecoxib Long-term Arthritis Safety Study (CLASS).

Results: The incidence of GI disorders of GCSB-5 was 23.7%. The annual rate of perforation, ulcer obstruction, or bleeding (PUB) incidence was 0.0%. The drop-out rate due to GI disorders following GCSB-5 use was 4.8%. Compared to celecoxib data from CLASS, the incidence of GI disorders (23.7% vs. 31.4%,

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$p < 0.001$), annual rate of PUB and gastroduodenal ulcers (0.0% vs 2.2%, $p = 0.004$), and drop-out rate due to GI disorders following GCSB-5 use were significantly low (4.8% vs 8.7%, $p < 0.001$). Efficacy was proven by significant improvements in Western Ontario McMaster Questionnaire (WOMAC) scale, Korean Knee Score (KKS), 100-mm pain visual analogue scale (VAS), and physician's global assessments of patient's response to therapy (PGART).

Conclusions: The safety and efficacy profile of GCSB-5 are comparable to celecoxib. These results indicate GCSB-5 is safe for a long-term treatment of knee OA patients.

Trial registration: ClinicalTrials.gov (NCT01604239).

1. Introduction

Osteoarthritis (OA) is a common disease that causes functional disability and considerable medical care expenses (Conaghan et al., 2008). Common pharmacologic treatments for OA include analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase-2 (COX-2) inhibitors (Manek and Lane, 2000). Despite the widespread use of NSAIDs, however, various adverse drug reactions (ADRs) have been reported, including gastrointestinal (GI) complications (American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines, 2002; Bombardier, 2002; Song et al., 2007). Further, OA requires long-term treatment, and prolonged use of NSAIDs can cause GI bleeding, gastric ulcers, and other serious GI complications (Gabriel et al., 1991; García Rodríguez and Jick, 1994; Hawkey, 1990).

A number of herbal medicines have been developed to treat OA (Angermann, 2005; Lung et al., 2004; Ownby et al., 2014; Park et al., 2013; Song et al., 2007; Yoo et al., 2014). One of these is GCSB-5 (Shinbaro®, Green Cross Corporation, Yongin, Korea), medicine approved in Korea at 2011, prepared from six purified oriental herbal extracts including *Saposhnikovia divaricata* Schischk, *Glycine max* Merrill, *Cibotium barometz* J. Smith, *Eucommiaulmoides* Oliver, *Achyranthes japonica* Nakai, and *Acanthopanax sessiliflorus* Seem (Lee and Cha, 2008; Lee and Cha, 2009; Cha and Lee, 2009; Cha and Lee, 2010). These herbs have played an important role in the medical care of for thousands of years in Korea (Heo, 1999; Lee, 1978). For example, *Acanthopanax sessiliflorus* and *Eucommiaulmoides* have been known for relieving oxidative stress. *Eucommiaulmoides* has been known to decrease interleukin-1β and tissue necrotic factor α. *Saposhnikovia divaricata* and *Cibotium barometz* also showed anti-inflammatory effect. These 6 medicinal herbal extracts used in producing GCSB-5 have demonstrated anti-inflammatory and analgesic effects (Kim et al., 2002, 2012; Lee et al., 2005), These results indicated that GCSB-5 could be promising for the treatment of OA. A phase III randomized double blind multicenter study revealed that GCSB-5 is comparable in safety and efficacy to the COX-2 inhibitor celecoxib (Celebrex®) (Park et al., 2013). The study, however, lasted only for 12 weeks and included only 198 patients, which does not seem to be adequate to determine the comparative safety of GCSB-5. Consequently, a longer term safety study in a larger number of patients is needed to establish the safety of GCSB-5 more decisively. Accordingly, a 24-week single-arm phase IV study involving patients with knee OA was conducted to determine the GI safety and efficacy of GCSB-5. Additionally, the GI safety results of GCSB-5 were compared with the data from the previously reported Celecoxib Long-term Arthritis Safety Study (CLASS) (Silverstein et al., 2000).

2. Methods

2.1. Study design

This study was a multicenter single-arm phase IV clinical trial. After a 2-week washout period, eligible patients were administered with the study drug for 24 weeks. The participants were monitored at weeks 4, 12, and 24 by out-patient visits, and by telephone at weeks 8, 16, and 20. The study protocol was approved by the institutional review boards of the participating hospitals (listed in eTable 1, Additional file 1) and a written informed consent was obtained from every participant enrolled.

2.2. Participants

Adult patients diagnosed with Kellgren and Lawrence stage I–III knee joint OA according to American College of Rheumatology (ACR) criteria were eligible to participate if OA symptoms were stable for three months. Patients were excluded from the study if they had other orthopedic diseases which could interfere with the efficacy evaluation, had used corticosteroids within the previous 12 weeks, had used psychotropic drugs or narcotic analgesics within the previous 4 weeks, had a hypersensitivity to any one of the six herbal ingredients, GI, renal, liver, or coagulation disorders, or if they participated in any other clinical trial within the previous 4 weeks (eTable 2, Additional file 1).

2.3. Treatment and concomitant medications

A capsule of GSCB-5 contains 300 mg of dried extracts of the mixture of six herbs in a fixed ratio; *Saposhnikovia divaricate* Schischk: *Glycine max* Merrill: *Cibotium barometz J.* Smith: *Eucommia ulmoides* Oliver: *Achyranthes japonica* Nakai: *Acanthopanax sessiliflorus* Seem = 4.444:2.778:2.778:1.389:4.444:4.444. GCSB-5 was manufactured with the following method. The six herbs were powdered and boiled for 3 h in distilled water. The resulting extract was ultra filtrated and the substances with molecular weight over 10,000 were excluded to obtain the final GCSB-5 extract. The filtrate was lyophilized and used for the manufacturing of GCSB-5 capsules.

Each participant took two GCSB-5 capsules (lot # 1518011, 300 mg each) twice per day (in the morning and evening) for 24 weeks. Low dose aspirin use for prevention of vascular events was allowed ($\leq$ 300 mg/day). Other concomitant medications that the investigator deemed would not affect the study outcomes were likewise allowed. Acetaminophen up to 2600 mg per day or 4550 mg per week was allowed as a rescue medication.

The following drugs and therapies were prohibited during the study period including the screening phase: topical medicines, analgesics, NSAIDs, and oral corticosteroids; intra-articular corticosteroid injection; anti-ulcer drugs (except transient antacid use); antibiotics for the treatment of *Helicobacter pylori* infection; proton pump inhibitors; H2 receptor antagonists; antineoplastics (e.g., methotrexate, tamoxifen); antidepressants; muscle relaxants; psychotropic drugs; narcotic analgesics; anticonvulsants; therapy to control pain including physical therapy and prolotherapy; and other over-the-counter drugs for the treatment of OA.

2.4. Outcome measures

The primary safety outcome measure was the incidence of

adverse events (AEs) related to the GI system. All of the AEs that occurred during the study period were collected at each visit by asking about any symptoms other than that of arthritis since the last visit. The AEs were collected regardless of the severity or relationship to the study drug. The AEs were classified according to the terminology of the Medical Dictionary for Regulatory Activities version 14.0 (MedRA 14.0) (Brown et al., 1999) and the AEs of GI disorders were classified according to the system organ class (SOC) from the MedRA 14.0. The secondary safety outcomes were the incidence of PUB (perforation, ulcer obstruction or bleeding, described in eTable 3 of Additional file 1) and the drop-out rate due to GI disorders. All participants with suspected PUB events were referred to GI specialists for PUB diagnosis, treatment, and related tests. For those participants, the investigator collected diagnostic and treatment information and submitted the GI event report form to the GI event committee (GEC) for adjudication. The GEC was comprised of independent GI specialists. The GEC adhered to the definitions of PUB from the MUCOSA trial (Silverstein et al., 1995) and the celecoxib new drug application. The incidence of PUB and gastroduodenal (GD) ulcers was summarized using an occurrence rate and an annual incidence rate. Additionally, the vital signs, clinical laboratory tests including blood tests, and physical examinations of study participants were evaluated and recorded. Based on the World Health Organization-Uppsala Monitoring Center causality assessment, ADRs were categorized into certain, probable/likely, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable.

Treatment efficacy was evaluated by measuring the change from baseline in the language-validated Western Ontario McMaster Questionnaire (WOMAC) scale score (Bae et al., 2001), the Korean Knee Score (KKS) (Kim et al., 2013), and the 100-mm pain visual analogue scale (VAS) score during ambulation. These scales were measured at baseline, and at 12- and 24-week outpatient visits. Physician's global assessments of patient's response to therapy (PGART) at weeks 12 and 24 were evaluated based on the assessments of WOMAC, KKS, and VAS. PGART was scored on a scale of 1–5 in which 1=excellent, 2=good, 3=fair, 4=none, and 5=poor (eTable 4, Additional file 1).

2.5. Sample size estimation

Sample size was calculated based on the hypothesis that the incidence of GI disorder in GCSB-5 use was not higher than that of celecoxib use reported in the previous study (Silverstein et al., 2000). The incidence of GI disorder for celecoxib observed in CLASS was 29.9%; accordingly, we aimed to determine if the incidence of GI disorder with GCSB-5 was lower than 29.9% in this single-arm study. Based on the previous Phase III clinical trial, AE incidence of GI disorder with GCSB-5 was 24.2% (Park et al., 2013). Hence, if the incidence of GI disorder with GCSB-5 had been 24.2%, the required sample size to demonstrate superiority of GCSB-5 in a one-sample study was 594 subjects for a 5% two-sided significance level and 90% power. Thus, assuming a drop-out rate of 20%, 743 participants were needed.

2.6. Statistical analysis

All participants who received at least one dose of the study drug were included in the safety analysis set (Fig. 1). The participants who took the study drug for at least 12 weeks and had the efficacy evaluation at week 12 were included in the full analysis (FA) set. The per protocol (PP) set consisted of the participants

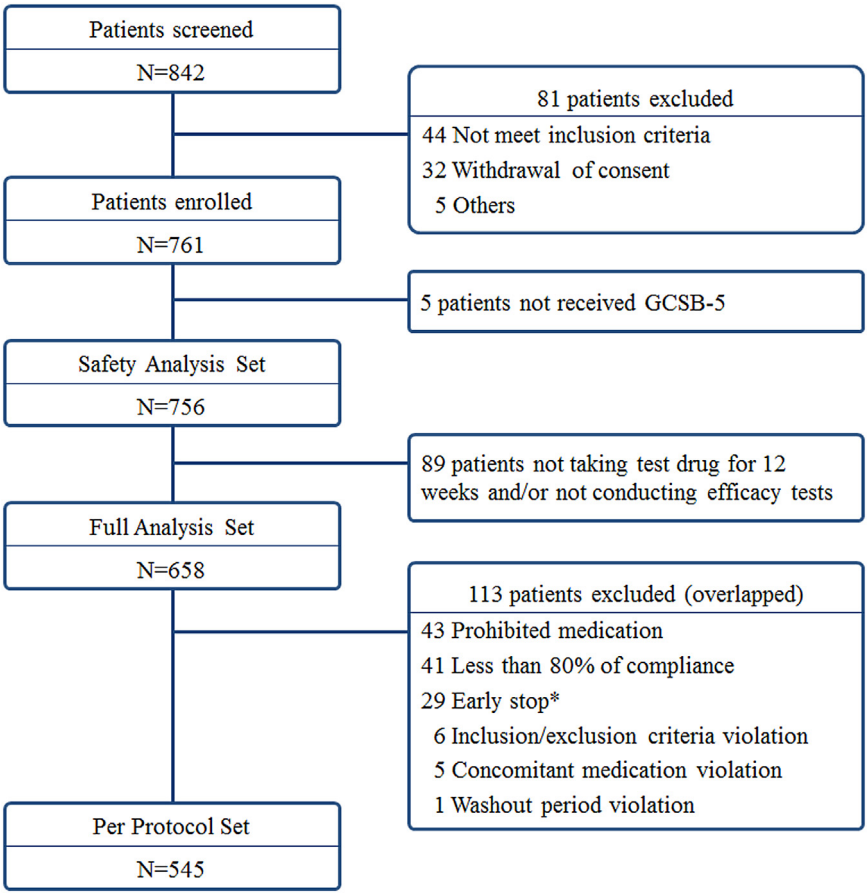

Fig. 1. Flowchart of patient disposition*, early stop including consent withdrawal (14), prohibited medication (7), failure of follow-up (4), AE or SAE (3) and others (1).

who completed the 24 week study without a major protocol violation. The efficacy analysis was conducted using the FA set and PP set. The last observation carried forward (LOCF) method was applied to the missing data for the efficacy analysis. To evaluate the changes from the baseline to the final visit, a paired *t*-test or Wilcoxon signed-rank test was used. All data analyses were performed using SAS®, and all statistical tests were two-sided and assumed a 5% significance level. Because the study was a single-arm study, the safety data were summarized using the 95% two-sided confidence interval (CI). For comparisons between the GCSB-5 and celecoxib safety data, an independent *t*-test or the Mann Whitney test was used for continuous data, whereas the Chi-square or Fisher's exact test was used for categorical data.

3. Results

3.1. Characteristics of the participants

A total of 842 patients were screened at 19 academic institutions from May 2012 to June 2013. Eighty-one patients failed to meet the inclusion criteria and 761 patients were enrolled (Fig. 1). The baseline characteristics of the 756 participants who received at least one dose of GCSB-5 are presented in Table 1. A total of 629 participants (82.7%) completed the GCSB-5 study (eTable 5, Additional file 1) and the overall compliance rate, calculated as the percentage of GCSB-5 consumed versus the number of capsules prescribed, was over than 95% at each interval (eTable 6, Additional file 1).

Table 1
Baseline characteristics of patients receiving GCSB-5 at least once (safety set).

Baseline variable	GCSB-5 (n=756)
Age, mean (range)	59.7 (22–81)
< 50 y, n (%)	78 (10.3)
50–60 < y, n (%)	290 (38.4)
60–70 < y, n (%)	285 (37.7)
≥ 70 y, n (%)	103 (13.6)
Gender, n (%)	
Male	153 (20.2)
Female	603 (79.8)
Smoking status, n (%)	
Non-smoking	711 (94.1)
Smoking	45 (6.0)
Alcohol use, n (%)	
None	589 (77.9)
Use	167 (22.1)
Height, mean (range), cm	157.8 (139–182.6)
Weight, mean (range), kg	62.1 (42.0–110.0)
Pregnancy test, n (%)	
Tested and negative	78 (10.3)
Not tested	678 (89.7)
Male	153 (22.6)
Postmenopausal	459 (67.7)
Surgically sterilized	66 (9.7)
Duration of disease, mean (SD), y	
Osteoarthritis	3.0 (4.2)
NSAID therapy at study entry, %	10.3
Aceclofenac	3.0
Meloxicam	2.8
Ibuprofen	0.8
Diclofenac	0.1
Other	8.3
Potential risk factor, %	
History of gastrointestinal bleeding	0.0
History of gastrointestinal ulcer	2.9
Helicobacter pylori infection, %	53.3
Concurrent medication, %	
Aspirin	8.9
Corticosteroids	2.9
Anticoagulants	11.5

SD, standard deviation; Min, minimum; Max, maximum
Note: Denominator of percentage is the number of subjects in the column.

3.2. Safety

Total 749 treatment emergent adverse events (TEAEs) from 333 participants (44.0%, 333/756) with 240 ADRs from 138 participants (18.3%, 138/756) were reported in the safety evaluation (Table 2). Of these, 632 TEAEs (84.4%) were mild cases, 102 (13.6%) moderate cases and 15 (2.0%) severe cases. Eleven participants (1.5%) experienced 11 serious adverse events (SAEs); 10 events were deemed not-related to the study drug by the investigators, and 1 event was considered unclassifiable (eTable 7, Additional file 1).

3.2.1. GI disorders

A total of 179 participants (23.7%, 179/756) reported experiencing a GI disorder-related TEAE at least once. The most commonly reported GI disorders were dyspepsia (11.1%), constipation (3.2%) and upper abdominal pain (2.8%) (Table 2). ADRs were observed in 138 (18.3%) participants. Among them, 108 participants experienced GI disorder-related ADRs. A serious ADR was reported in 1 case, which was “reflux esophagitis.”

Thirty suspected PUB cases from 15 participants were referred to the GEC, and the GEC adjudicated that none of the cases met PUB criteria (eTable 3, Additional file 1). Of the 30 suspected PUB cases, 17 cases from 11 participants were deemed “non-PUB”; 15 cases from 9 participants were judged to be miscellaneous GI symptoms, and 2 cases from 2 participants were found to be non-ulcer bleeding. The remaining 13 cases from 4 participants were all adjudicated to be not clinically significant (NCS) AEs. Hence, the annual incidence rate of PUB and GD ulcers was 0% among the 756 participants (Table 3).

Of the initial cohort of 756 participants who received at least one dose of the study drug, 132 were dropped during the study period. Among the 132 participants, 36 (4.8%, 36/756) dropped out of the study because of GI disorders (Table 4). The results of the subgroup analysis for GI disorders showed that participant's age, gender, duration of OA, use of low dose aspirin, use of rescue medication, presence of *Helcobacter pylori* infection, and NSAID use at baseline did not significantly affect the incidence of GI disorder or the drop-out rate. Participants with high compliance showed a lower incidence of GI disorder and a lower drop-out rate (Table 4).

3.2.2. Other adverse events

The TEAEs and ADRs are summarized in Table 2. The incidence of dyspepsia was highest at 11.1%, followed by nasopharyngitis (8.2%), headache (4.0%), and constipation (3.2%). None of the changes in the laboratory tests or physical examinations observed between baseline and 24 weeks were considered clinically meaningful. No significant differences were observed in any of the vital sign categories. Among the categories of laboratory tests, the red blood cell count, hemoglobulin, hematocrit, platelet count, prothrombine time, cholesterol level and glucose level were

Table 2
Incidence of treatment emergent adverse events and adverse drug reactions (safety set).

Adverse events	GCSB-5 (N=756)					
	TEAEs			ADRs		
	Number of events	Number of subjects	Percentage of subjects (%)	Number of events	Number of subjects	Percentage of subjects (%)
Total incidence	**749**	**333**	**44.0**	**240**	**138**	**18.3**
Gastrointestinal disorders	**302**	**179**	**23.7**	**171**	**108**	**14.3**
Dyspepsia	110	84	11.1	71	57	7.5
Constipation	24	24	3.2	15	15	2.0
Abdominal pain, upper	26	21	2.8	18	14	1.9
Nausea	22	18	2.4	14	10	1.3
Abdominal pain	11	11	1.5	5	5	0.7
Abdominal distension	9	9	1.2	5	5	0.7
Gastritis	9	9	1.2	3	3	0.4
Diarrhea	9	7	0.9	5	3	0.4
Abdominal discomfort	7	7	0.9	6	6	0.8
Gastritis atrophic	7	7	0.9	4	4	0.5
Reflux esophagitis	7	7	0.9	4	4	0.5
Vomiting	6	6	0.8	1	1	0.1
Dry mouth	5	5	0.7	3	3	0.4
Gastroesophageal reflux disease	5	5	0.7	3	3	0.4
Others[a]	45	44	5.8	14	13	1.7
Infections and infestations	**109**	**84**	**11.1**	**2**	**2**	**0.3**
Nasopharyngitis	74	62	8.2	1	0.1	1
Cystitis	10	8	1.1	–	–	–
Others[a]	25	24	3.2	1	0.1	1
Musculoskeletal and connective tissue disorders	**85**	**66**	**8.7**	**9**	**8**	**1.1**
Back pain	20	18	2.4	–	–	–
Musculoskeletal pain	14	13	1.7	2	2	0.3
Pain in extremity	13	12	1.6	–	–	–
Arthralgia	6	6	0.8	1	1	0.1
Myalgia	6	5	0.7	1	1	0.1
Musculoskeletal stiffness	5	5	0.7	1	1	0.1
Others[a]	20	20	2.6	4	3	0.4
Nervous system disorders	**84**	**59**	**7.8**	**18**	**11**	**1.5**
Headache	45	30	4.0	9	5	0.7
Dizziness	20	17	2.2	9	7	0.9
Others[a]	18	17	2.2	–	–	–
Skin and subcutaneous tissue disorders	**48**	**40**	**5.3**	**14**	**12**	**1.6**
Pruritus	22	17	2.2	8	6	0.8
Urticaria	8	8	1.1	3	3	0.4
Others[a]	18	17	2.2	3	3	0.4
General disorders and administration site conditions	**33**	**22**	**2.9**	**14**	**11**	**1.5**
Face edema	7	6	0.8	5	4	0.5
Others[a]	26	21	2.8	9	7	0.9
Miscellaneous[b]	**88**	**74**	**9.8**	**12**	**10**	**1.3**

[a] Less than 5 patients for each category (based on TEAEs) were included to others.
[b] For miscellaneous, all subjects in each category (based on TEAEs) were less than 5.

significantly different between base line and 24-week. However, the changes of these parameters were not large (eTable 8, Additional file 1). No significant differences were observed in any of other laboratory categories. In addition, no significant abnormal results were observed upon physical examination.

3.2.3. Comparison of the safety results with the CLASS data (Silverstein et al., 2000)

The incidence of GI disorder with GCSB-5 was significantly lower than that of the historical rate reported for celecoxib (23.7% vs. 31.4%, $p < 0.001$). The difference in annual rate of PUB and GD ulcers between GCSB-5 and celecoxib was highly significantly (0.0% vs. 2.2%, $p = 0.004$). The drop-out rate also was significantly lower in the current study than in the celecoxib study (4.8% vs. 8.7%, $p < 0.001$).

3.3. Efficacy

Efficacy analysis revealed significant improvement of all parameters (Fig. 2). The WOMAC and KKS scores significantly improved between baseline and 24 weeks. Additionally, GCSB-5 use significantly reduced the pain VAS score by 18.9 ± 25.5 in FA set ($p < 0.001$) and 20.2 ± 24.9 in PP set ($p < 0.001$). According to the PGART scale, the treatment effect at 24 weeks was excellent in 146 participants (22.2%), good in 390 participants (59.3%), fair in 100 participants (15.2%), none in 18 participants (2.7%), and poor in 4 participants (0.6%) (eTable 9, Additional file 1). The treatment response rate at 24 weeks, which was composed of excellent, good, and fair in this study, was 96.7%.

4. Discussion

This study was conducted to evaluate the safety and efficacy of

Table 3
Gastroduodenal ulcers and ulcer complications (safety set).

	GCSB-5[a] (N=756)		
	No. of events	**No. of subjects**	**Percentage of subjects, %**
Total number of cases adjudicated for ulcer or ulcer complication	**30**	**15**	**2.0**
Number of adjudicated cases not meeting the definition of a gastroduodenal ulcer or ulcer complication			
Esophageal disease	0	0	–
Gastroduodenitis	0	0	–
Colonic or small bowel disease	0	0	–
Nonulcer bleeding	2	2	0.3
Miscellaneous gastrointestinal symptoms	15	9	1.2
Anemia	0	0	–
Cholelithiasis	0	0	–
Subtotal	**17**	**11**	**1.5**
Number of adjudicated cases meeting the definition of a gastroduodenal ulcer or ulcer complication			
Gastroduodenal ulcers	0	0	–
Ulcer complications	0	0	–
Bleeding	0	0	–
Perforation	0	0	–
Ulcer obstruction	0	0	–
Subtotal	**0**	**0**	–
NCS	**13**	**4**	**0.5**
Annualized rate[b] (PUB+Gastroduodenal ulcer)	**0**	**0**	–
Annualized rate[b] (PUB)	**0**	**0**	–

PUB, perforation, ulcer obstruction, or bleeding; NCS, not clinically significant; Patient days, Days from first medication date to last medication date or to onset date of adverse event

[a] Number of case are displayed as number of subjects [number of events].
[b] (Events/patient days/365.25)*100.

24-week use of GCSB-5 treatment in a large number of OA patients. GCSB-5 taken twice daily for 24 weeks showed a favorable safety and efficacy profile and was well tolerated. Only a small proportion of participants experienced AEs with a few serious AEs.

The incidence of GI disorders with 24-week administration of GCBS-5 was low. In addition, no PUB and GD ulcers were observed. Conversely, the prevalence of GD ulcers is approximately 15–45% in patients who administered NSAIDs regularly (Laine et al., 1999; Laine, 2001). The components of GCSB-5 are thought to have active antioxidant properties, to decrease nitric oxide production, and to yield analgesic and anti-inflammatory effects (Park et al., 2013). Among several actions, the anti-inflammatory effects of *Eucommia ulmoides*, a component of GCSB-5, were established by elucidation of the suppression of COX-2 levels in macrophages (Kim et al., 2009). Although it is impossible to compare directly the results with previous studies because the study designs were not standardized, the absence of PUB and GD ulcers in this study implies that GCSB-5 is safe with regard to the GI system. Further, the incidence of ADRs was 18.3% in the present study, which was consistent with previous findings (Park et al., 2013). Despite the long-term administration of GCSB-5, no increases in the incidence of ADRs were observed in the present study. Additionally, the incidence of GI ADRs in patients treated with celecoxib in other studies was 22–25% (Hochberg et al., 2011; Park et al., 2013). In this study, however, only 14.2% of the patients treated with GCSB-5 for 24 weeks reported GI ADRs. The ADR-related discontinuation rate (3.8%) was also lower than the rates previously reported in tolerability studies with other NSAIDs (4.8–8.0%) (Fan et al., 2009; Hochberg et al., 2011; Lehmann et al., 2005). Collectively, the results of this study indicate that GCSB-5 is associated with lower rates of GI disorders, including serious complications such as PUB or GD ulcers.

In accordance with a previous study (Park et al., 2013), we found that GCSB-5 appeared efficacious for the treatment of OA. The minimal clinically important differences (MCID) in WOMAC for OA of the knee or hip are reportedly 9.1–11.1 points (Ehrich et al., 2000; Tubach et al., 2005). In this study, the significant improvement in WOMAC scores (-8 at week 12 and -12 at week 24) was comparable to reported MCID values. In a previous study, the improvement in 100 mm pain VAS for knee OA was 19.9 over the baseline value (Tubach et al., 2005). Hence, the improvement in VAS score in the present study (18.9) was also comparable to the previous report.

In this study, the secondary goal was to compare the GCSB-5 GI safety data with the previously reported CLASS celecoxib safety data. In this study, the incidence of PUB or GD ulcers and the dropout rate due to GI disorders were all significantly lower than the corresponding values in CLASS ($p < 0.001$ and $p < 0.001$, respectively). Overall, this study showed that the frequency of GI disorders caused by GCSB-5 was much lower, including incidence of serious complications such as PUBs or GD ulcers. The direct comparison of the data from the two studies, however, should have significant limitations, including differences in the proportion of patients using NSAIDs at the study onset (81.4% in CLASS data vs 10.3% in the present study) and the duration of OA(10.3 years in CLASS vs. 3.0 years in this study). The use of NSAIDs at study onset may have increased the occurrence of GI disorders, and an increased duration of OA may also have led to an increased incidence of GI disorders. In this study, differences in the risk of GI disorders between aspirin users and non-users were not significant ($p=0.370$) (Table 4). However, the corresponding increase from 29.9% to 37.0% in the celecoxib patients according to aspirin use was significant ($p < 0.001$) (Silverstein et al., 2000). Therefore, the differences in the baseline prognostic factors between the GCSB-5 and the celecoxib safety data may diminish the significance of the differences in GI safety results between the current GCSB-5 data and CLASS celecoxib data. Nevertheless, it should be noted that none of the participants with GCSB-5 in the present study experienced PUB or GD ulcers, which suggests that GCSB-5 is safe to use in OA patients. Nonetheless, the safety and efficacy of GCSB-5 should be assessed in a more diverse population of OA patients.

The strengths of this study are that a high proportion of the study population (629/756, 83.2%) completed the GCSB-5 study for 24 weeks, and the overall compliance rate was very high (92.3%). Most prospective studies designed to assess the efficacy and safety of NSAIDs in patients with OA reported a 28–35% discontinuation rate (Bello et al., 2015; Chopra et al., 2013; Silverstein et al., 2000). Hence, the current results imply that the high rate of study completion seems to be due to the low rate and reduced severity of AEs. Consequently, the current safety study and prior efficacy study indicate that GCSB-5 could be an alternative medication for the treatment of OA.

5. Conclusion

This 24-week open-label study demonstrated that the safety and efficacy profile of a new therapeutic agent, GCSB-5, for patients with osteoarthritis are comparable to a previously published study with celecoxib. The results of this study indicate that GCSB-5 can be used for a long-term treatment of patients with knee OA with a comparable gastrointestinal safety profile to celecoxib.

Table 4
Subgroup analysis: gastrointestinal disorders and drop-out (safety set).

	Gastrointestinal disorders			**Drop-out**		
All		**N=756**			**N=132**	
Gastrointestinal disorders, n (%)		179 (23.7)			36 (4.8)[1]	
Two-sided 95% confidence interval		(20.7, 26.9)			(3.4, 6.5)	
Age group	**≥ 65 years (N=187)**	**< 65 years (N=569)**	**p-value**	**≥ 65 years (N=187)**	**< 65 years (N=569)**	**p-value**
Gastrointestinal disorders, n (%)	37 (19.8)	142 (25.0)	0.149[2]	9 (4.8)	27 (4.8)	0.970[2]
Two-sided 95% confidence interval	(14.3, 26.2)	(21. 5, 28.7)		(2.2, 8.9)	(3.2, 6.8)	
Gender	**Male (N=153)**	**Female (N=603)**	**p-value**	**Male (N=153)**	**Female (N=603)**	**p-value**
Gastrointestinal disorders, n (%)	28 (18.3)	151 (25.0)	0.080[2]	5 (3.3)	31 (5.1)	0.401[3]
Two-sided 95% confidence interval	(12.5, 25.4)	(21.6, 28.7)		(1.1, 7.5)	(3.5, 7.2)	
Duration of osteoarthritis	**≥ 5 years (N=193)**	**< 5 years (N=563)**	**p-value**	**≥ 5 years (N=193)**	**< 5 years (N=563)**	**p-value**
Gastrointestinal disorders, n (%)	52 (26.9)	127 (22.6)	0.216[2]	14 (7.3)	22 (3.9)	0.060[2]
Two-sided 95% confidence interval	(20.8, 33.8)	(19.2, 26.2)		(4.0, 11.9)	(2.5, 5.9)	
Aspirin	**Taken (N=67)**	**Not Taken (N=689)**	**p-value**	**Taken(N=67)**	**Not Taken (N=689)**	**p-value**
Gastrointestinal disorders, n (%)	19 (28.4)	160 (23.2)	0.345[2]	5 (7.5)	31 (4.5)	0.239[3]
Two-sided 95% confidence interval	(18.0, 40.7)	(20.1, 26.6)		(2.5, 16. 6)	(3.1, 6.3)	
Rescue medication	**Taken (N=604)**	**Not Taken (N=152)**	**p-value**	**Taken (N=604)**	**Not Taken (N=152)**	**p-value**
Gastrointestinal disorders, n (%)	144 (23.8)	35 (23.0)	0.833[2]	26 (4.3)	10 (6.6)	0.239[2]
Two-sided 95% confidence interval	(20.5, 27.5)	(16.6, 30.5)		(2.8, 6.2)	(3.2, 11.8)	
H. pylori	**Positive (N=403)**	**Negative (N=351)**	**p-value**	**Positive (N=403)**	**Negative (N=351)**	**p-value**
Gastrointestinal disorders, n (%)	102 (25.3)	77 (21.9)	0.278[2]	22 (5.5)	14 (4.0)	0.345[2]
Two-sided 95% confidence interval	(21.1, 29.9)	(17.7, 26.6)		(3.5, 8.2)	(2.2, 6.6)	
NSAIDs use at baseline	**Taken (N=78)**	**Not Taken (N=678)**	**p-value**	**Taken (N=78)**	**Not Taken (N=678)**	**p-value**
Gastrointestinal disorders, n(%)	22 (28.2)	157 (23.2)	0.321[2]	3 (3.9)	33 (4.9)	1.000[3]
Two-sided 95% confidence interval	(18.6, 39.5)	(20.0, 26.5)		(0.8, 10.8)	(3.4, 6.8)	
Compliance	**90% or higher (N=597)**	**Less than 90% (N=159)**	**p-value**	**90% or higher (N=597)**	**Less than 90% (N=159)**	**p-value**
Gastrointestinal disorders, n (%)	124 (20.8)	55 (34.6)	< 0.001[2]	10 (1.7)	26 (16.4)	< 0.001[2]
Two-sided 95% confidence interval	(17.6, 24.3)	(27.2, 42.5)		(0.8, 3.1)	(11.0, 23.0)	

Note: Denominator of percentage is the number of subjects in the column.

[a] Percentage of patients who dropped-out due to GI disorder in total participants.
[b] Chi square test.
[c] Fisher's Exact test.

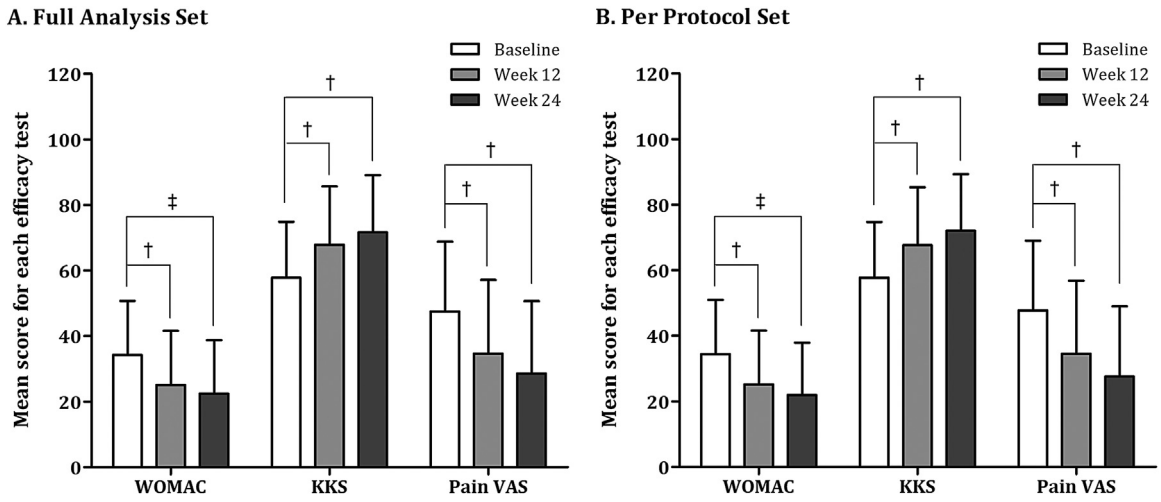

Fig. 2. The changes of WOMAC, KKS, and pain VAS score from baseline to week 24 on full analysis set and per protocol set. Bars and error bars represent mean scores and standard deviation of each test, respectively. GCSB-5 significantly improved all efficacy tests on full analysis set (A) and per protocol set (B). †, $p < 0.001$ with Wilcoxon signed-rank test; ‡, $p < 0.001$ with Paired *t*-test.

Author Contributions

Conception and design:
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Final approval of the article:
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Statistical expertise:
Yong-Beom Park.
Obtaining of funding:
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Collection and assembly of data:
All authors.

Role of the funding source

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Conflict of interests

The authors declare that they have no competing interests.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jep.2016.05.031.

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